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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WENDA C. CARLYLE, SHEILA J. KELLY,
and MATTHEW F. OGLE

Appeal 2008-002766
Application 09/186,810
Technology Center 3700

Decided: August 31, 2009

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims directed to a biomedical device comprising natural tissue or a biological matrix and a covalently bound polypeptide growth factor. We have jurisdiction under 35 U.S.C. § 6(b).

BACKGROUND

Prosthetic devices, such as artificial heart valves, etc., "are used to repair or replace damaged or diseased organs, [and] tissues . . . [and] must be generally biocompatible since they are typically implanted for extended periods of time" (Spec. 1: 14-18).

"Prostheses can be constructed from natural materials such as tissue, synthetic materials [such as metals, graphite and polyester] or a combination thereof (*id.* at 1: 23-28). Tissue based prostheses have a number of advantages over synthetic prostheses, but also a number of disadvantages. For example, tissues used in prostheses are typically "fixed by crosslinking" with glutaraldehyde, which "provides mechanical stabilization" and "removes antigenic sites that could result in . . . rejection of the prosthesis" (Spec. 8: 30-34). However, "evidence suggests that glutaradehyde fixation can contribute to calcification" (*id.* at 2: 25-33), and calcification is "a major cause of degeneration" (*id.* at 2: 27).

"Another major disadvantage of tissue based prostheses is the failure of such devices to be self-maintaining . . . [due to the] [in]ability of viable cells to populate the implanted tissue and to carry out maintenance functions" (*id.* at 3: 5-9). Moreover, "nonviable cells can be sites for calcium deposition . . . [but] [i]ntact tissue with viable cells has natural protection against calcification" (*id.* at 2: 34 to 4: 4).

The present invention "pertains to a prosthesis comprising a substrate and a polypeptide growth factor crosslinked to said substrate, the polyepeptide growth factor being effective to stimulate the association of viable cells with the substrate" (*id.* at 3: 20-24).

STATEMENT OF THE CASE

Claims 1, 3, 4, 8-10, 13, 15, 34, 35, 38-40, 45, and 46 are on appeal, while claims 28, 29, 33, and 41-44 have been allowed, and claims 14, 36, and 37 have been objected to.

Claims 1 and 46 are representative of the subject matter on appeal:

1. A biomedical device comprising a natural tissue and a polypeptide growth factor associated with the natural tissue by covalent bonding using crosslinking agents, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, wherein the crosslinking agents comprise at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the natural tissue, the polypeptide growth factor associated with the natural tissue being effective to stimulate association of viable cells with the substrate.

46. A prosthesis comprising a substrate, the substrate not including a linker molecule attached thereto, and a polypeptide growth factor crosslinked to the substrate by covalent bonding using crosslinking agents, wherein the crosslinking agents comprise at least two aldehyde functional groups that form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the substrate, the polypeptide growth factor associated with the substrate being effective to stimulate association of viable cells with the substrate.

The Examiner relies on the following evidence:

Cahalan	US 5,308,641	May 3, 1994
Goldstein	US 5,613,982	Mar. 25, 1997
Bayne	EP 0 476 983 A1	Mar. 23, 1992

The Examiner rejected the claims as follows:

(A) Claims 1, 3, 4, 8, 9, 15, 45, and 46 under 35 U.S.C. § 102(b) as anticipated by Cahalan.

(B) Claim 10 under 35 U.S.C. § 103(a) as unpatentable over Cahalan and Goldstein.

(C) Claim 13 under 35 U.S.C. § 103(a) as unpatentable over Cahalan and Bayne.

(D) Claim 46 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

(E) Claim 46 under 35 U.S.C. § 112, second paragraph, as indefinite.

(F) Claims 1, 8, 10, 13, 15, 34, 35 and 38-40 under the doctrine of obviousness-type double patenting over co-pending Application No. 09/014,187.

We reverse the anticipation and obviousness rejections, and affirm the written description, indefiniteness, and double patenting rejections.

ANTICIPATION

Issue (A)

The issue raised by the rejection is whether Appellants have shown that the Examiner erred in finding that Cahalan describes a biomedical device comprising a substrate (a natural tissue or a biological matrix) and a polypeptide growth factor, where a crosslinking agent with at least two aldehyde functional groups is linked directly to the substrate and the growth factor through covalent bonds.

Findings of Fact

FF1 The Examiner rejected claims 1, 3, 4, 8, 9, 15, 45, and 46 as anticipated by Cahalan (Ans. 5-7).

FF2 Independent claim 1 is directed, in pertinent part, to a biomedical device comprising a polypeptide growth factor crosslinked to

natural tissue by covalent bonds using crosslinking agents comprising at least two aldehyde functional groups. The aldehyde groups on the crosslinking agents "form covalent bonds to link the crosslinking agent directly with the polypeptide growth factor and the natural tissue[.]"

FF3 Independent claim 45 is similar to claim 1, except that the biomedical device comprises a polypeptide growth factor crosslinked to a "biological matrix."

FF4 Glutaraldehyde is an example of a crosslinking agent with at least two aldehyde functional groups (Spec. 9: 1-3).

FF5 "Tissues can be fixed by crosslinking . . . .[which] provides mechanical stabilization . . . [and] removes antigenic sites that could result in . . . rejection of the prosthesis" (Spec. 8: 30-34).

FF6 Glutaraldehyde is typically used for fixation (Spec. 9: 1-2).

FF7 According to the Specification, joining a polypeptide growth factor (e.g., vascular endothelial growth factor (VEGF)) to a substrate "can involve direct attachment . . . or chemical binding" (Spec. 13: 30-31).

FF8 An example of "[d]irect attachment entails combining the substrate, such as a tissue substrate, with a solution of the [growth factor] VEGF. . . . it has been discovered that the VEGF can associate with glutaraldehyde crosslinked biological tissue" (Spec. 14: 3-7).

FF9 "The chemical binding of VEGF can involve covalent bonding to the surface of the substrate with reactive agents such as . . . general crosslinking agents. A typical procedure . . . makes use of glutaraldehyde, which crosslinks proteins by way of two aldehyde groups" (Spec. 17: 5-11). "Since glutaraldehyde is typically used for fixation of some biocompatible materials, the non-specific crosslinking to bind the VEGF to the

biocompatible material can be performed simultaneously with fixation of the tissue" (*id.* at 17: 11-15).

FF10 Cahalan teaches that the biocompatibility of a biomaterial (also referred to as a "substrate" or a "solid surface") intended for use as an implantable medical device can be improved by immobilizing various 'biomolecules' (such as cell adhesion molecules or growth factors) on the surface of the biomaterial to promote the attachment and growth of a normal cell layer on the device (Cahalan, col. 1: 39-44; col. 4, ll. 32-33).

FF11 However, "methods [that] immobilize the biomolecule closely to the biomaterial surface . . . reduc[e] the availability of the biomolecule for interaction with . . . cells intended to adhere to the biomolecule" (Cahalan, col. 2: 7-10).

FF12 Cahalan discloses an implantable medical device comprising "an aminated substrate [i.e., a biomaterial], a polyalkylimine [spacer] covalently attached to the aminated substrate and a crosslinking agent which is at least difunctional in aldehyde groups" (Cahalan, col. 3, ll. 4-7), and a biomolecule. The crosslinking agent provides "light crosslinking of the polyalkylimine" and also provides "sufficient aldehyde linkages at the interface between the biomolecule and the polyalkyimine to provide light crosslinking with the attached biomolecule" (*id.* at col. 3, ll. 16-20).

FF13 "The polyalkylimine is covalently bonded to the solid surface . . . by contacting amine groups on the solid surface with an activating agent which contains at least two aldehyde groups and then contacting the activated surface with the polyalkylimine" (Cahalan, col. 3, ll. 21-26).

FF14 The activating agent used to activate the solid surface can be the same as the crosslinking agent used to crosslink the polyalkylimine, e.g., glutaraldehyde (Cahalan, col. 3, ll. 9-10, 25-29).

FF15 This results in a polyalkylimine "spacer which is strongly attached to the [biomaterial]" and "which presents a stable platform for the attachment of the biomolecule and thereby prevents the attached biomolecule from being buried in the spacer layer" (Cahalan, col. 2, ll. 64-68).

FF16 Appellants contend (App. Br. 13), and the Examiner does not dispute, that polyalkylimines do not have aldehyde functional groups.

Principles of Law

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

During examination, the PTO must interpret terms in a claim using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

Analysis

All of the claims on appeal require crosslinking agents with at least two aldehyde functional groups, where the aldehyde groups on the crosslinking agents form covalent bonds to link the crosslinking agents

directly with the polypeptide growth factor and the substrate (i.e., the natural tissue of claim 1, or the biological matrix of claim 45).

The Examiner finds that Cahalan joins "the molecules of an aldehyde and [a] polyalkylimine . . . to form a crosslinking agent that directly attaches polypeptide growth factor to the substrate" (Ans. 6). "Said another way, the dialdehyde molecule (call it molecule A) is used to both attach the polyalkylimine (call it molecule B) to the solid surface . . . and to attach the polyalkylimine to the biomolecule. . . . Thus, the crosslinking agent(s) as claimed are met by the molecular sandwich(es) (A-B-A) of Cahalan" (*id.*).

However, the Specification teaches that "chemical binding of VEGF can involve covalent bonding to the surface of the substrate with reactive agents such as . . . glutaraldehyde, which crosslinks proteins by way of two aldehyde groups" and "non-specific crosslinking to bind the VEGF to the biocompatible material can be performed simultaneously with fixation of the tissue" (FF9). The broadest reasonable interpretation of "directly" linking the crosslinking agent with the polypepide growth factor and the substrate, consistent with Specification, is that the aldehyde groups on the crosslinker attach the growth factor to the substrate without the participation of any other intervening non-dialdehyde molecule, regardless of whether it's called a crosslinker, a linker, or a spacer.

Cahalan uses glutaraldehyde, a dialdehyde crosslinker, to attach a growth factor to a biological substrate. However, the dialdehyde crosslinker is not linked directly to the growth factor and the substrate, because another molecule, a polyalkylimine, which does not have aldehyde groups (FF16), is interposed between the growth factor and the substrate (FF13-FF15).

Conclusions of Law

Appellants have shown that the Examiner erred in finding that Cahalan describes a biomedical device comprising a substrate (a natural tissue or a biological matrix) and a polypeptide growth factor, where a crosslinking agent with at least two aldehyde functional groups is linked directly to the substrate and the growth factor through covalent bonds.

OBVIOUSNESS

Issues (B) and (C)

The Examiner rejected claim 10 as unpatentable over Cahalan and Goldstein (Ans. 7), and claim 13 as unpatentable over Cahalan and Bayne (*id.* at 8).

Claim 10 depends from claim 1 and requires specific types of natural animal tissues. Claim 13 also depends from claim 1 and specifies that the polypeptide growth factor is VEGF.

The dispositive issue raised by these rejections is whether Appellants have shown that the Examiner erred in concluding that a biomedical device comprising a substrate (natural animal tissue for claim 10) and a polypeptide growth factor (VEGF for claim 13), where a crosslinking agent with at least two aldehyde functional groups is linked directly to the substrate and the growth factor through covalent bonds, would have been obvious over the combined teachings of the prior art.

Analysis

Claims 10 and 13 depend from claim 1, and therefore require all of the elements of claim 1. Cahalan does not disclose a biomedical device where a

crosslinking agent with at least two aldehyde functional groups is linked directly to the substrate and the growth factor through covalent bonds, and this deficiency is not remedied by Goldstein or Bayne.

Conclusions of Law

Appellants have shown that the Examiner erred in concluding that a biomedical device comprising a substrate (natural animal tissue for claim 10) and a polypeptide growth factor (VEGF for claim 13), where a crosslinking agent with at least two aldehyde functional groups is linked directly to the substrate and the growth factor through covalent bonds, would have been obvious over the combined teachings of the prior art.

WRITTEN DESCRIPTION and INDEFINITENESS

Issues (D) and (E)

The Examiner rejected claim 46 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement (Ans. 3), and also rejected claim 46 under 35 U.S.C. § 112, second paragraph, as indefinite (*id.* at 4).

Claim 46 is similar to claim 1 in requiring a crosslinking agent with at least two aldehyde functional groups linked directly to the substrate and the growth factor through covalent bonds, but additionally includes the negative proviso: "the substrate not including a linker molecule attached thereto[.]"

The written description rejection is couched in terms of whether there is "original support for the preclusion of a linker molecule . . . when the polypeptide growth factor is covalently bonded to the surface" through a crosslinker (Ans. 3-4).

The indefiniteness rejection states that "preclusion of a linker molecule is confusing . . . in that a molecule on the tissue must link to the crosslinking agent to bind it thereto" (Ans. 4).

The dispositive issue in both rejections is whether the Specification explicitly or inferentially differentiates between "linkers" and "crosslinkers."

Findings of Fact

FF17 The Specification gives examples of "linkers" and "crosslinkers," but does not explicitly define either term.

FF18 The Specification indicates that polypeptide growth factors can be attached to a substrate using "general crosslinking agents," which include reactive agents such as glutaraldehyde and epoxies (Spec. 17: 5-20).

FF19 The Specification also indicates that growth factors can be attached to a substrate using "linkers" including "antibodies and other specific binding reagents" (Spec. 19: 6-18).

FF20 Claim 46 requires "crosslinking agents compris[ing] at least two aldehyde functional groups that form covalent bonds to *link* the crosslinking agent directly with the polypeptide growth factor and the substrate" (emphasis added).

FF21 A crosslinking agent with at least two aldehyde functional groups is a specific type of linker.

Analysis

The crosslinker required by claim 46 contains aldehyde functional groups that form covalent bonds that *link* it directly with the polypeptide growth factor and the substrate (FF20). The Specification gives examples of "crosslinkers" and "linkers," but does not explicitly define either term, or otherwise indicate that the terms don't overlap. Thus, the crosslinker

required by the claim is simply a specific type of linker (FF21). It may be that Appellants intended to exclude linkers *other* than those with at least two aldehyde functional groups from the claim. However, the claim, as written, is indefinite and lacks adequate support in the Specification, because it excludes linkers generally, but includes a particular type of linker.

Conclusions of Law

The Specification does not differentiate between "linkers" and "crosslinkers." Claim 46, which excludes linkers generally, but includes a particular type of linker, fails to comply with the written description requirement, and is also indefinite.

DOUBLE PATENTING

The Examiner provisionally rejected claims 1, 8, 10, 13, 15, 34, 35, and 38-40 under the doctrine of obviousness-type double patenting as unpatentable over claims 1, 2, 9, 14, and 21 of copending Application No. 09/014,087 (Ans. 5).

Appellants indicate their willingness to file a terminal disclaimer "upon allowance of both the present Application and Application 09/014,087" (App. Br. 11).

Appellants have not established that the Examiner erred in provisionally rejecting the claims under the doctrine of obviousness-type double patenting.

SUMMARY

(A) The rejection of claims 1, 3, 4, 8, 9, 15, 45, and 46 under 35 U.S.C. § 102(b) as anticipated by Cahalan is reversed.

(B) The rejection of claim 10 under 35 U.S.C. § 103(a) as unpatentable over Cahalan and Goldstein is reversed.

(C) The rejection of claim 13 under 35 U.S.C. § 103(a) as unpatentable over Cahalan and Bayne is reversed.

(D) The rejection of claim 46 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement is affirmed.

(E) The rejection of claim 46 under 35 U.S.C. § 112, second paragraph, as indefinite is affirmed.

(F) The rejection of claims 1, 8, 10, 13, 15, 34, 35 and 38-40 under the doctrine of obviousness-type double patenting over co-pending Application No. 09/014,187 is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED-IN-PART

Ssc

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